



Chapter 4

Results and discussion

Full term infants comprise of 41 male (51.25%) and 39 female (48.75%) infants. Mean gestational age was 38.7 ± 1.2 wks (37-41 wks) and birth weight was 3197 ± 336 g (2,580-4,320 g). The baseline characteristics of 40 very low birth weight premature infants are shown in table 1. There were 21 male (52.5%) and 19 female (47.5%) infants. Mean gestational age was 28.9 ± 1.9 wks (24-32 wks) and mean birth weight was 1123.1 ± 218.1 g (670-1,490 g).

The serum levels of vitamin A were higher in full term infants than in VLBW premature infants (0.79 ± 0.42 Vs 0.68 ± 0.32 $\mu\text{mol/L}$) but not statistical significant ($p=0.19$). Mean of maternal serum vitamin A levels of full term infants was 2.08 ± 0.59 $\mu\text{mol/L}$ and of VLBW premature infants was 2.39 ± 0.76 $\mu\text{mol/L}$. The mean serum level of vitamin A in full term infants was 38% of maternal blood level compare to 28% of maternal blood level in VLBW premature infants.

At birth, fewer infants in the full term infants had serum vitamin A levels less than 0.7 $\mu\text{mol/L}$ compared to very low birth weight premature infants (50 Vs 52.5%). Only

one of full infants compared to 5 of very low birth weight premature infants had a level below 0.35 $\mu\text{mol/L}$ (1.25 Vs 12.5%).

Table 1 Baseline characteristics of the VLBW premature infants

Characteristics	VLBW premature infants (n=40)
Birth weight(g) mean \pm SD(min-max)	1,123.1 \pm 218.1 (670-1,490 g)
Gestational age(wk) mean \pm SD(min-max)	28.9 \pm 1.9 (24-32 wk)
Small for gestational age: no.(%)	7 (17.5)
Male sex: no.(%)	21(52.5)
Antenatal corticosteroid: no.(%)	29(72.5)
Apgar scores at 1, 5 min	2,6
Respiratory distress syndrome no.(%)	34(85)
Respiratory status at 24 hr	
Mechanical ventilation no.(%)	28(70)
Mean airway pressure (cmH ₂ O) mean \pm SD	7.1 \pm 1.7

Table 2 Serum vitamin A levels of full term, premature infants and mothers

	Serum vitamin A levels($\mu\text{mol/L}$)
Full term infants (n=80)	0.79 ± 0.42
Mothers of full term infants (n=80)	2.08 ± 0.59
Premature infants (n=40)	
d0	0.68 ± 0.32
d7	0.92 ± 0.38
d14	0.96 ± 0.36
d28	0.76 ± 0.30
Mothers of premature infants (n=40)	2.39 ± 0.76

Serum vitamin A levels of premature infants were lower than full term infants but not significant. The mean level of vitamin A in full term infants was 38% of maternal blood level compare to 28% of maternal blood level in premature infants. This finding suggested that very low birth weight premature infants are prone to have low level of vitamin A because of less transplacental transport from mothers. More than half of very low birth weight premature infants had vitamin A levels less than $0.7 \mu\text{mol/L}$ which

indicated of vitamin A deficiency stage and 12.5% had a level below $0.35 \mu\text{mol/L}$ which is suggestive of severe vitamin A deficiency compared to 1.25% of full term infants. At 28 days of age, despite parenteral nutrition and enteral feeding, 45% of very low birth weight premature infants had vitamin A levels less than $0.7 \mu\text{mol/L}$ and 5% had a level below $0.35 \mu\text{mol/L}$.

Safety of vitamin A supplementation in VLBW premature infants

Signs of potential vitamin A toxicity that could not be explained by other factors (e.g., intraventricular hemorrhage, post-hemorrhagic hydrocephalus causing a full fontanelle) were not identified in all premature infants enrolled in the study.

Results and Discussion of vitamin A supplementation for prevention of BPD

Of the 85 very-low-birth-weight premature infants who were screened for enrollment, 5 were ineligible (four infants were considered to be terminally ill and 1 parent denied consent). The baseline characteristics of the infants in both groups were similar (Table 3) Mean Birth weight of infants in vitamin A and control group was $1,152.8 \pm 203.6 \text{ g}$ (680-1,460 g) and $1,123.1 \pm 218.1 \text{ g}$ (670-1,490g). Mean gestational age of infants in vitamin A and control group was $29.0 \pm 1.7 \text{ wk}$ (24-32 wk) and $28.9 \pm 1.9 \text{ wk}$ (24-32 wk).

Table 3 Baseline characteristics of the premature infants

Characteristics	Vitamin A (n=40)	Control (n=40)
Birth weight(g): mean \pm SD	1,152.8 \pm 203.6 (680-1,460 g)	1,123.1 \pm 218.1 (670-1,490g).
Gestational age(wk): mean \pm SD	29.0 \pm 1.7(24-32 wk)	28.9 \pm 1.9(24-32 wk)
Small for gestational age: no.(%)	8 (20)	7 (17.5)
Male sex: no.(%)	20(50)	21(52.5)
Antenatal corticosteroid: no.(%)	29(72.5)	29(72.5)
Apgar scores at 1, 5 min	2,6	2,6
Respiratory status at 24 hr		
Mechanical ventilation no.(%)	27(67.5)	28(70)
Mean airway pressure cm of water(cmH ₂ O)	7.0 \pm 1.7	7.1 \pm 1.7
Time from birth to first treatment (hr)	49.1 \pm 27.2	49.3 \pm 17.4

The mean serum vitamin A levels before administration of the vitamin A supplement were similar in both groups ($0.68 \pm 0.32 \mu\text{mol/L}$ in the control group Vs $0.66 \pm 0.35 \mu\text{mol/L}$ in the vitamin A group). The mean serum level of vitamin A was significant higher in the vitamin A supplemented infants than the control infants on day 7 (1.41 ± 0.48 Vs $0.92 \pm 0.38 \mu\text{mol/L}$, p.00), day 14 (1.48 ± 0.90 Vs $0.96 \pm 0.36 \mu\text{mol/L}$, p.001) and day 28 (1.42 ± 0.63 Vs $0.76 \pm 0.30 \mu\text{mol/L}$, p.00) after vitamin A supplementation. Fewer infants in the vitamin A group had serum vitamin A levels less than $0.7 \mu\text{mol/L}$ on day 28 compared to the control group (10 Vs 45%). None of infant in the vitamin A group compared to 5% of infants in the control group had a level less than $0.35 \mu\text{mol/L}$ at 28 days. (Table 4)

Table 4 Serum vitamin A levels of the premature infants before and after supplementation

	Vitamin A (n=40)	Control (n=40)	P value
Serum vitamin A levels before supplementation ($\mu\text{mol/L}$) mean \pm SD	0.66 \pm 0.35	0.68 \pm 0.32	.95
Serum vitamin A level on day 7 after supplementation ($\mu\text{mol/L}$) mean \pm SD	1.41 \pm 0.48	0.92 \pm 0.38	.00
Serum vitamin A level on day 14 after supplementation ($\mu\text{mol/L}$) mean \pm SD	1.48 \pm 0.90	0.96 \pm 0.36	.001
Serum vitamin A level on day 28 after supplementation ($\mu\text{mol/L}$) mean \pm SD	1.42 \pm 0.63	0.76 \pm 0.30	.00

Supplementation with vitamin A associated with significant reduction in duration of intubation (10.8 ± 3.1 days in vitamin A supplemented Vs 26.1 ± 6.4 days in control group, $p= 0.03$), days on oxygen therapy (29.8 ± 5.1 days in vitamin A supplemented Vs 58.2 ± 9.1 days in control group, $p= 0.008$) and length of hospital stay (61.9 ± 4.2 days in vitamin A supplemented Vs 88.3 ± 7.2 days in control group, $p= 0.002$). Bronchopulmonary dysplasia at 36 weeks' postmenstrual age was fewer in the vitamin A supplemented infants than in the control infants but not statistically significant (22.5 Vs 35% relative risk 0.71 ; 95% confidence interval 0.40 to 1.26 ; $p=0.21$). There were also non-significant trends toward reduction in risk of retinopathy of prematurity (7.5% in vitamin A supplemented Vs 17.5% in control group, relative risk 0.41 ; 95% confidence interval 0.11 to 1.43 ; $p= 0.07$), nosocomial sepsis (35% in vitamin A supplemented Vs 42.5% in control group, relative risk 0.83 ; 95% confidence interval, 0.52 to 1.3 ; $p= 0.43$), patent ductus arteriosus (47.5% in vitamin A supplemented Vs 57.5% in control group, relative risk 0.81 ; 95% confidence interval, 0.52 to 1.26 ; $p= 0.37$), and severe intraventricular hemorrhage grade 3 or 4 (0 in vitamin A supplemented Vs 5% in control group, ; $p= 0.152$). (Table 5)

Table 5 Bronchopulmonary dysplasia (BPD) and other outcomes of the VLBW premature infants

Outcomes	Vitamin A (n=40)	Control (n=40)	P value
BPD at 36 wk post menstrual age: no.(%)	9 (22.5)	14 (35)	0.21
Death before discharge: no.(%)	2(5)	1(2.5)	0.56
Retinopathy of prematurity: no.(%)	3 (7.5)	7 (17.5)	0.07
Hospital acquired sepsis: no.(%)	14 (35)	17 (42.5)	0.43
Necrotizing enterocolitis: no.(%)	7(17.5)	8(20)	0.57
Patent ductus arteriosus no.(%)	19(47.5)	23(57.5)	0.37
Severe intraventricular hemorrhage grade 3 or 4 no.(%)	0(0)	2(5)	0.152
Days on endotracheal tube (days) mean \pm SE	10.8 \pm 3.1	26.1 \pm 6.4	.03
Days on oxygen therapy (days) mean \pm SE	29.8 \pm 5.1	58.2 \pm 9.1	.008
Length of hospitalization (days) mean \pm SE	61.9 \pm 4.2	88.3 \pm 7.2	.002

Very low birth weight premature infants are prone to have vitamin A deficiency because of less transplacental transport from mothers, moreover, premature infants usually have inadequate intake from enteral feeding for several weeks after birth as well as poor gastrointestinal absorption, and unreliable delivery of parenteral vitamin A. The present study attempted to define serum vitamin A levels and the role of vitamin A supplementation for prevention of bronchopulmonary dysplasia in very low birth weight premature infants in the northeastern part of Thailand and confirmed that intramuscular vitamin A supplementation can increase the serum level of vitamin A in this susceptible population. Forty-five percent of premature infants in the control group had vitamin A levels less than 0.7 $\mu\text{mol/L}$ which indicate of vitamin A deficiency compared to 10% in the supplement group at 28 days. Furthermore, none of the infants in vitamin A group had a level below 0.35 $\mu\text{mol/L}$ which is suggestive of severe vitamin A deficiency compared to 5% of infants in the control group at 28 days.

The dose of vitamin A supplementation in this study was similar to previous studies and there was no clinical evidence of vitamin A toxicity.

The results of a large multicenter trial and meta-analysis found that vitamin A supplementation to very low birth weight infants is associated with benefit in terms of

reducing death or oxygen requirement at one month of age and oxygen requirement at 36 weeks post menstrual age.^(16,17) The present study demonstrated that fewer infants in the vitamin A supplementation group required oxygen at 36 weeks postmenstrual age but not statistical significant (22.5 Vs 35% relative risk 0.71; 95% confidence interval 0.40 to 1.26; p= 0.21) Duration of intubation, oxygen therapy and length of hospital stay are significant shorter in vitamin A supplemented infants.

Low plasma vitamin A levels have been associated with development of ROP in some studies.^(12,18) Pooled data show a trend towards a reduction in ROP, culture positive nosocomial sepsis in infants supplemented with vitamin A but non-statistical significant.⁽¹⁷⁾ The incidence and severity of intraventricular hemorrhage is higher in infants with low hepatic storage of vitamin A⁽⁴⁾, however, supplementation was not significantly reduced incidence of intraventricular hemorrhage.⁽¹⁶⁾ Vitamin A accelerates the development of oxygen induced constriction of the ductus arteriosus postnatally in the rat model.⁽¹⁹⁾ However, in a small group of ventilator dependent preterm infants weighing 500–1,500 g, intramuscular vitamin A did not affect spontaneous closure of PDA.⁽²⁰⁾ Supplementation with vitamin A in VLBW premature infants in the present study was associated with non-significant trends toward reduction in risk of retinopathy of prematurity (7.5 Vs 17.5 % in vitamin A supplemented and control group, relative risk

0.41 ; 95% confidence interval 0.11 to 1.43; $p = 0.07$), nosocomial sepsis (35 Vs 42.5%, relative risk 0.83 ; 95% confidence interval, 0.52 to 1.3; $p = 0.43$), patent ductus arteriosus (47.5 Vs 57.5 %, relative risk 0.81; 95% confidence interval, 0.52 to 1.26; $p = 0.37$), and severe intraventricular hemorrhage (0 Vs 5 %; $p = 0.152$) .